Remarks

Claims 1 and 11-14 were pending in the subject application. By this Amendment, claims 1 and 11-14 have been cancelled, and new claims 15-26 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 15-26 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants and the applicants' representative wish to thank Examiner Haddad and Examiner Nolan for the courtesy of the telephonic interview conducted with the undersigned and Dr. Nasser Chegini on May 20, 2004, regarding claims 1 and 11-14, and the rejection under 35 U.S.C. §112, first paragraph. The remarks and amendments set forth herein are consistent with the substance of the interview and the Examiner's Interview Summary mailed to the applicants on May 24, 2004, and are believed to address the outstanding issues as discussed during the interview.

By this Amendment, claims 1 and 11-14 have been cancelled and claims 15-26 have been added. Support for claims 15 and 26 can be found, for example, at page 3, lines 8-19 and 23, of the specification, the abstract, and the claims as originally filed. Support for claims 16 and 17 can be found, for example, at page 3, lines 22 and 23, of the specification, and the claims as originally filed. Support for claims 18 and 19 can be found, for example, at page 3, lines 24 and 25, of the subject specification, and the claims as originally filed. Support for claim 20 can be found, for example, at page 1, lines 1-2, page 3, lines 11-18, 21, and 22, of the subject specification, and the claims as originally filed. Support for claims 21-23 can be found, for example, at page 1, lines 5-7, page 3, lines 8-11, and page 4, lines 27-30, of the subject specification, and the claims as originally filed. Support for claims 24 and 25 can be found, for example, at page 4, lines 27-30, page 7, lines 14-15, of the subject specification, and the claims as originally filed.

Claims 1 and 11-14 are rejected under 35 U.S.C. §112, first paragraph, as non-enabled. The applicant respectfully submits that the claimed subject matter is fully enabled by the subject specification. However, as indicated above, the applicants have cancelled claims 1 and 11-14 and added new claims 15-26. As discussed during the telephonic interview, new claim 15 recites a method for reducing adhesion formation, comprising administering a therapeutic formulation

comprising TIMP-1 antibodies, or Fab fragments thereof, to a patient at risk of adhesion formation, wherein the therapeutic formulation is administered in an amount effect to reduce adhesion formation. The applicants respectfully submit that a reasonable correlation exists between the scope of claims 15-26 and the scope of enablement provided.

The applicants respectfully submit that the subject specification enables methods for reducing adhesions using the recited formulation. Although the applicants submit that the Patent Office has not met its initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, submitted herewith for the Examiner's consideration is a Declaration under 37 C.F.R. §1.132 by Dr. Nasser Chegini, with Exhibits A-N, wherein Dr. Chegini addresses issues raised during the telephonic Examiner interview. As the Examiner is aware, the determination of enablement must be based on evidence as a whole. As indicated in MPEP § 2164.05, "A declaration or affidavit is, itself, evidence that must be considered" (emphasis in original). MPEP § 2164.05 states:

> To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works.

As Dr. Chegini indicates in his Declaration, adhesions are abnormal fibrous scar tissues that create connections between tissues or organs that are normally separated, or between tissues and foreign materials. Further,

> [i]t has become clear that excess production and deposition of the extracellular matrix (ECM) which occurs during normal wound healing is a key factor in producing tissue fibrosis, including the development of adhesions. A coordinated balance between the production of the endoproteases known as matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) is an important step in tissue remodeling...Thus, for normal healing to occur, the availability of these molecules must be optimal. Inhibition, interruption, or excess expression of these molecules seems to be responsible for failure in normal healing, resulting in either impairment of tissue formation (a non-healing or chronic wound) or excess tissue formation (scar/adhesion development). Further information regarding adhesions can be obtained from the review paper submitted herewith as Exhibit B, of which I am the author (*Frontiers in Bioscience*, e91-115, April 1, 2002).

Chegini Declaration, page 2, section 2.

As Dr. Chegini states at pages 2-3, section 3, of his Declaration, adhesions can be induced by infection, hemorrhage, foreign bodies (such as sutures and implants), ischemia, and/or trauma (such as surgical injury). In addition to intra-peritoneal or intra-abdominal adhesions, adhesions can also occur following musculoskeletal surgery, ophthalmic surgery, orthopedic surgery, surgery of the central nervous system, and cardiovascular surgery, for example. As Dr. Chegini explains, intra-peritoneal adhesions are more often reported because surgeons routinely conduct peritoneal dialysis, laparotomy, and laparoscopy are routine procedures that frequently induce adhesion formation. Furthermore, the surface of intra-peritoneal organs and the parietal peritoneum together represent the largest surface within the body (almost equaling that of the skin). Complications of intra-peritoneal adhesions are also very severe (*e.g.*, bowel obstruction, infertility, and chronic pelvic pain), which further highlights the problem. The applicants respectfully submit that the experimental findings regarding surgically-induced peritoneal adhesions may be extrapolated to adhesions induced by infection, hemorrhage, foreign bodies (such as sutures and implants), ischemia, and/or trauma in other areas of the body. As explained by Dr. Chegini,

> Peritoneal wound healing is not dissimilar from wound healing in other soft tissues of the body, however. In fact, it is well understood that a local inflammatory response and tissue remodeling are underlying processes which occur during normal wound healing throughout the soft tissues of the body, including the peritoneal cavity. It is also generally accepted that failure of these processes to properly orchestrate is necessary for formation of adhesions, whether the adhesion is induced by infection, ischemia, or trauma. The outcome is the same regardless of stimulus or anatomical site—fibrous scar tissue (adhesion). Thus, surgical adhesions of the peritoneal cavity are the accepted experimental model for adhesions in general.

Chegini Declaration, page 3, section 4.

TIMP-1 is expressed in many tissues, inhibiting MMP proteolytic activity and regulating cell migration. Thus, as stated by Dr. Chegini, "because adhesions form as a result of excessive cellular migration and ECM deposition, there is no reason to doubt the applicability of the method of the subject invention to reduce adhesions in general, whether they are induced by infection, ischemia, or trauma, and regardless of anatomical site."

During the telephonic interview, the Examiner requested an explanation for the variability in levels of TIMP-1 in peritoneal fluid. As Dr. Chegini explains at page 5, section 6, of his Declaration, the level of TIMP-1 in peritoneal fluids is influenced by variables such as the expression and release of factors by the resident cells of the peritoneal fluid, the contribution of serum-derived factors to the peritoneal fluid, and the rate of peritoneal fluid turnover (and, thus, the timing of the sampling). The variability of factors present in peritoneal fluid and peritoneal fluid turnover are well documented, as evidenced by Exhibits G-L, which accompany Dr. Chegini's Declaration. Therefore, the factors detected in peritoneal fluid reflect the peritoneal environment in general. In contrast, tissue samples taken from the serosal tissue surface provide specific information regarding the sites where adhesions form. Furthermore, as Dr. Chegini points out, "the level of TIMP-1 in serosal tissues may be more relevant to intervention using a function-blocking antibody because there is more unbound TIMP-1 (*i.e.*, not complexed with MMP-1) in the tissues, and unbound TIMP-1 is more susceptible to recognition and interference by the anti-TIMP-1 antibody administered in accordance with the method of the invention."

Exhibits M and N (Chegini *et al.*, *Fertility and Sterility*, 76(6):1212-1219 (December 2001); and Chegini *et al.*, *Fertility and Sterility*, 76(6):1207-1211 (December 2001)), which accompany Dr. Chegini's Declaration, further support the enablement of the invention as currently claimed. Exhibits M and N describe experiments investigating the levels of MMP-1 and TIMP-1 in serosal tissue of intraperitoneal organs and adhesions, and peritoneal fluids and sera. Exhibits M and N describe experimental data contained within the patent application, as well as additional data. As shown in Figure 4B of Exhibit M, in an evaluation of ten patients with adhesions, the TIMP-1 protein content in adhesions was significantly higher than that in intact parietal peritoneum (P=.05) and skin (P=.03). Figure 5C of Exhibit M shows that adhesions have a lower ratio of MMP-1 to TIMP-1 compared with intact parietal peritoneum. As indicated by Dr. Chegini at page 6, section 7, of his Declaration, this supports the premise that adhesions form due to an environment that favors matrix deposition rather than degradation. Figure 2 of Exhibit N also provides evidence that the peritoneal fluid levels of TIMP-1 in subjects with extensive adhesions are higher compared with those in subjects without adhesions, as discussed at column 2 of pate 1208.

The applicants submitted the following scientific publications with the previous Amendment filed on December 1, 2003, which demonstrate the successful use of antibodies that interfere with the function of their target antigens *in vivo*: Rothlein R. *et al.*, "Treatment of Inflammation with Anti-ICAM-1", *Res. Immunol.*, 1993, 144(9):735-739; Wegner C. *et al.*, "Efficacy of Monoclonal Antibodies Against Adhesion Molecules in Animal Models of Asthma", *Agents Actions Suppl.*, 1993, 43:151-162; Zhang R. *et al.*, "Anti-ICAM-1 Antibody Reduces Ischemic Cell Damage After Transient Middle Cerebral Artery Occlusion in the Rat", *Neurology*, 1994, 44(9):1747-1751; Maguire H. *et al.*, "Neutralizing Anti-IL-10 Antibody Upregulates the Induction and Elicitation of Contact Hypersensitivity", *J. Interferon Cytokine Res.*, 1997, 17(12):763-768; Iimuro Y. *et al.*, "Antibodies to Tumor Necrosis Factor Alfa Attenuate hepatic Necrosis and Inflammation Caused by Chronic Exposure to Ethanol in the Rat", *Hepatology*, 1997, 26(6):1530-1537; Walter U. *et al.*, "Generation and Characterization of a Novel Adhesion Function Blocking Monoclonal Antibody Recognizing Both Rat and Mouse E-Selectin", *Hybridoma*, 1997, 16(4):355-361; Petit A. *et al.*, "Neutralizing Antibodies Against Epidermal Growth Factor and ErbB-2/neu Receptor Tyrosine Kinases Down-Regulate Vascular Endothelial Growth Factor Production by Tumor Cells *In Vitro* and *In Vivo*", *Am. J. Pathol.*, 1997, 151(6):1523-1530; van Deventer S. and Comoglio L., "Monoclonal Antibody Therapy of Inflammatory Bowel Disease", *Pharm. World Sci.*, 1997, 19(2):55-59; Lorenz H. *et al.*, "*In Vivo* Blockade of TNF-α by Intravenous Infusion of a Chimeric Monoclonal TNF-α Antibody in Patients with Rheumatoid Arthritis", *J. Immunol.*, 1996, 156(4):1646-1653; Henricks P. and Nijkamp F., "Pharmacological Modulation of Cell Adhesion Molecules", *Eur. J. Pharmacol.*, 1998, 344(1):1-13; and Yamasaki Y. *et al.*, "New Therapeutic Possibility of Blocking Cytokine-Induced Neutrophil Chemoattractant on Transient Ischemic Brain Damage in Rats", *Brain Res.*, 1997, 759(1):103-111. As demonstrated by the foregoing scientific publications, function-blocking antibodies have been utilized to interfere with the activities of various adhesion molecules and cytokines.

Furthermore, submitted with the IDS December 1, 2003 was the Forough *et al.* publication (Forough, R. *et al.*, "Generating Antibodies Against Secreted Proteins Using Vascular Smooth Muscle Cells Transduced with Replication-Defective Retrovirus", *BioTechniques* 20:694-701, 1996), which describes an anti-TIMP-1 antibody capable of inhibiting the activity of TIMP-1 *in vivo*

(see lines 25-28 of the abstract and pages 699-701). Various other means of inhibiting TIMP-1 have also been utilized in the art, such as anti-sense RNA and targeted gene disruption, as demonstrated by the Khokha *et al.* publication and Alexander and Werb publication, respectively (Khokha R. *et al.*, "Antisense RNA—Induced Reduction in Murine TIMP Levels Confers Oncogenicity on Swiss 3T3 Cells", *Science, New Series*, 243(4893):947-950, 1989; Alexander, C. and Werb, Z., "Targeted Disruption of the Tissue Inhibitor of Metalloproteinases Gene Increases the Invasive Behavior of Primitive Mesenchymal Cells Derived from Embryonic Stem Cells *In Vitro*", *J. Cell Biology*, 118(3):727-739, 1992), which were also submitted with the IDS.

While page 6 of the Office Action acknowledges that anti-TIMP-1 antibodies are available and the foregoing publications provide some support that antibodies may be used in therapeutic treatment purposes in certain situations, it also states "...however the method of using the anti-TIMP-1 in vivo for prevention or remediation of surgical adhesions is not disclose. [sic] Therefore, these articles/patent do not address the point at issue". The applicants respectfully submit that if this were the standard for enablement, an invention could not be simultaneously enabled and novel. Rather, it is well settled in patent law that the standard is whether undue experimentation would be required by one of ordinary skill in the art in order to practice the claimed invention, given the benefit of the subject application. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Antibodies have also been utilized *in vivo* within the context of fibrosis and adhesion reduction. Submitted herewith for the Examiner's consideration, are U.S. Patent Nos. 5,571,714 (Dasch *et al.*), 5,783,185 (Dasch *et al.*), and 5,972,335 (Ferguson *et al.*). These patents, which issued in 1996, 1998, and 1999, respectively, describe methods for reducing fibrosis using an antibody that neutralizes transforming growth factor-beta 1 (TGF-β1) and transforming growth factor-beta 2 (TGF-β2) *in vivo*. For example, administration of anti-PAI-1 antibodies has been reported to reduce the incidence of adhesion formation in surgically-induced peritoneal injury (Falk K. *et al.*, *Br. J. Surg.*, 88:286-289 (2001), submitted with Dr. Chegini's Declaration as Exhibit C). Dr. Lena Holmdahl, a co-author of the Falk *et al.* publication, is a co-inventor of the subject application.

Accordingly, the applicants respectfully submit that, given the teaching of the specification and the state of the art in antibody production and antibody therapeutics, one of ordinary skill in the art could carry out the claimed methods without the need for undue experimentation. In view of the

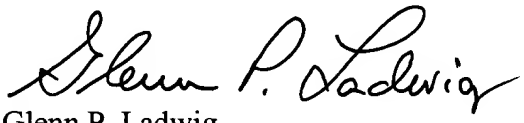
foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition and Fee for Extension of Time
Declaration under 37 C.F.R. 1.132 by Dr. Chegini, with Exhibits A-N
U.S. Patent Nos. 5,571,714; 5,783,185; and 5,972,335